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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,446	04/22/2005	Christoph De Haen	B-0497 PUS	1688

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
04/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,446	DE HAEN ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10, 13-22* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/11/2009 has been entered.

Claims 1-10 and 13-22 are pending.

Claims 1-9 and 17-22 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 10 and 13-16 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical characteristics and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (Federal register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 column 3) and (see MPEP 2164).

In the instant case, the claims encompass molecular entities molecular entities imparting diagnostic utility, wherein the molecular entities include, but are not limited to, derivatives of chelating agents for or chelates of radionucleotides, paramagnetic metal ions or luminescent metal ions. Thus, the claims broadly encompass a genus of derivatives of chelators which have diagnostic utility. The specification teaches that suitable molecular entities imparting diagnostic utility comprise suitable derivatives of chelating agents for or chelate of radionucleotides, paramagnetic metal ions or luminescent metal ions (page 10, lines 23-26). The state of the art at the time the invention was made recognize that there are a variety of chelating agents which have diagnostic utility. For example, Rocklage et al. (5,833,947, 1998) teach that there are a variety of suitable chelates for the formation of paramagnetic metal chelate MS contrast agents including, but not limited to, DTPA, DTPA-BMA, DTPA-BMO, DOTA, DO3A, HP-DO3A, and OTTA (column 5, line 54 to column 6, line 5). Thus, while the state of the art recognize chelating agents, the specification does not appear to describe how far a chelating agent can deviate from what is known. A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cNDA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb.

13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of derivatives that encompass the genus nor does it provide a description of structural features that are common to the genus. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure is insufficient to describe the genus. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of the encompassed genus, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 10 and 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lui et al. (Journal of Labelled Compounds and Radiopharmaceuticals 1998; XLI: 37-45) in view of Getz et al (Analytical Biochemistry 1999; 273: 73-80) and Maurer et al. (WO 02/056907 A2, IDS) as evidenced by Cruse and Lewis (Cruse, Julius and Lewis, Robert. Illustrated Dictionary of Immunology Boca Raton, FL, 1995, of record).

Lui et al. teach a method of direct labeling of monoclonal antibodies and methods of evaluating reducing agents. For example, the reference teaches reducing monoclonal antibody 3H11 Fab fragment with DTT followed by labeling with ^{99m}Tc, e.g. diagnostic moiety (page 43, ^{99m}Tc labeling of 3H11 McAb and its Fab fragment). Yet, the reference teaches that there was rapid loss of ^{99m}Tc from antibodies in the presence of challenging reagents containing –SH groups such as cysteine (page 44, last paragraph).

Lui et al. does not explicitly teach that the reducing agent is TCEP. Nor does Lui et al. teach the reaction conditions as recited in claims 13-16.

Getz et al. teach a comparison of sulfhydryl reductants tris(2-carboxyethyl)phosphine, e.g., TCEP, and dithiothreitol, e.g, DTT, for use in Protein Chemistry. In particular, Getz et al. teach TCEP offer several advantages over DTT and is the superior reductant when labeling proteins (page 80, 1st column, last paragraph).

Maurer et al. teach a method of coupling Fab fragments to Qβ capsid proteins comprising combining a first solution of a reduced fab fragment generated by reacting a concentration of a Fab fragment, 2.5 mg/mL, at a pH of 7.2 with different concentration (0-1000μM, e.g. 0 mM to 1mM) of either dithiothreitol (DTT) or tricarboxyethylphosphine (TCEP) for 30 minutes at 25°C and a second solution comprising a SMPH derivatized Qβ capsid protein, wherein the final concentration of the protein and Fab were 1.14 mg/mL and 1.78 mg/mL respectively and the reaction proceeded overnight at 25°C (pages 140-141, Example 16). Thus, while Maurer et al. do not explicitly report the Fab concentration in μM or the conjugating moiety concentration in mM, e.g., micromoles/microliter or millimoles/mL, the concentration of the Fab will depend on its molecular weight reported in g/mol which as evidenced by Cruse and Lewis is 47,000 KD, e.g., 47,0000 g/mol

(Definition of Fab fragment). Thus, the μM concentration used by the prior art reference is 53μM (See Exhibit I for conversion). In addition, while Maurer et al. do not explicitly report the stoichiometric ratio between the Fab fragment and Qβ capsid protein to be in the range of 1.95 to 2.05, the claimed stiochiometric moar ratio will depend on the molecular weight reported in g/mol which for the reduced Fab fragment is 23,500 Kd and for the protein appears to be about 15,000Kd (see figure 21, marker for Qβ capsid protein. Thus, the stiochiometric ratio used by the prior art is 1 Qβ capsid protein's per 1 Fab fragment (see Exhibit II for conversion).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method taught by Lui et al. to include TCEP as the reducing agent in view of the teachings of Getz et al. and Maurer et al. One would have been motivated to do so because in view of the teachings of Getz et al. those of skill in the art recognize that TCEP is the superior reductant for labeling proteins, and further, as taught by Maurer et al., can effectively reduce fab fragments. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying the method taught by Lui et al. to include TCEP as the reducing agent in view of the teachings of Getz et al. and Maurer et al. , one would achieve a method for reduction of a fab fragment for direct labeling with ^{99m}Tc.

Moroever, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the reaction conditions for TCEP reduction in view of teh teachings of Maurer et al. One would have been motivated to do so because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by optimizing the concentration of the Fab fragment and resultant conjugate moiety, one would achieve the optimal reaction conditions for the conjugation.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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